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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/691,711	10/23/2003	Rolf Banholzer	1/1148-2-C2	2056

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MICHAEL P. MORRIS
BOEHRINGER INGELHEIM CORPORATION
900 RIDGEBURY ROAD
P. O. BOX 368
RIDGEFIELD, CT 06877-0368

EXAMINER	
COPPINS, JANET L	
ART UNIT	**PAPER NUMBER**
1626	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/691,711	BANHOLZER ET AL.	
	Examiner	Art Unit	
	Janet L. Coppins	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 9-21* is/are pending in the application.

4a) Of the above claim(s) *9-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-4 and 9-21 pending in the instant application.

Information Disclosure Statement

2. Applicants' Information Disclosure Statements (IDS), submitted October 23, 2003 and February 6, 2004, have been considered by the Examiner. Please refer to the signed copies of Applicants' PTO-1449 forms, attached to the instant Office Action.

Election/Restrictions

3. Applicant's election without traverse of Group I in the reply filed on January 26, 2007, is acknowledged. Claims 9-21 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the preparation of the crystalline compounds with the specific DSC and IR spectra found in Figures 1 and 2 of the specification, does not reasonably provide enablement for any crystalline monohydrate of tiotropium bromide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case, the claims are read as a polymorphic form of tiotropium bromide, named "crystalline tiotropium bromide monohydrate" with no XRDP or other physical properties provided. The phrase "crystalline ...monohydrate" is Applicants' own terminology and might include any monohydrate form of triotropium bromide, since no physical data have been provided.

The nature of the invention

The nature of the invention is a crystalline monohydrate form of tiotropium bromide.

The state of the prior art and the predictability or lack thereof in the art

It is the state of the prior art that polymorphism is the existence of different solid forms (modifications) of a compound which have the same chemical composition but different structures and thus different physical and sometimes also chemical properties (Concise Encyclopedia Chemistry, 1993). It is also the state of the art that any polymorph (including

compounds that are characterized by the DSC and IR data in Figures 1 and 2 of the specification) might include other forms without the same X-ray diffraction patterns. It is the state of the prior art that under any given pressure and temperature, other than the conversion points, only one modification is stable, the form with the lowest vapor pressure. Often the conversion rate in the solid phases is so slow that even modifications, which are unstable under normal conditions, can be kept for a long time in their metastable state. This conversion rate can depend on the rate of temperature change or pressure change (Concise Encyclopedia Chemistry 1993). The predictability or lack thereof in the art is that there can be multiple forms of a solid in existence and these polymorphs are created by varying crystallization processes that began with varying starting materials, utilize varying solvents, varying temperatures and varying reaction times.

There is no method that exists to predict the polymorphs of a solid compound with significant certainty (Rouhi, page 32). Preparing a crystalline form of any compound will cause a specific crystalline form, if in the metastable state, to always resort back to the most thermodynamically stable form.

Furthermore, in addition to exhibiting polymorphism, many compounds form crystalline solvates in which the solvent molecule is an integral part of the crystal structure. Just as every polymorph has its one characteristic X-ray diffraction pattern, so does every solvate. (U.S. Pharmacopia #23, page 1843) Also, sometimes the differences in the diffraction patterns of different polymorphs are relatively minor, and must be very carefully evaluated before a definitive conclusion is reached (U.S. Pharmacopia, page 1843).

The amount of direction or guidance present and

the presence or absence of working examples

The only direction or guidance present for the instant process is the preparation of the specific crystalline forms defined by the data found in Figures 1 and 2 of the instant specification.

The breadth of the claims

The breadth of the claims is the preparation of an unspecified monohydrate (with any XRDP) of tiotropium bromide.

The quantity of experimentation needed and the level of the skill in the art

The quantity of experimentation is extremely high. One would need to prepare crystalline hydrates of tiotropium bromide by many different methods to obtain multiple polymorphic forms, while the specification only provides methods and direction to the process of the preparation of the specific crystalline forms with the DSC and IR spectra found in Figures 1 and 2 of the instant specification. The level of skill in the polymorph art is high. However, without a showing or guidance as to how to make the specific monohydrate form claimed, besides the crystalline forms as described in the specification, it would require undue experimentation to figure out how to prepare the unspecified polymorph "crystalline... monohydrate" the claimed process. The Examiner recommends incorporating specific physical properties for Applicants' "monohyrdrate" into the claim (i.e. X-RDP, DSC, or IR data), so as to distinguish it from other crystalline monohydrate forms.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-4 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the

invention. Regarding the chemical name of "monoclinic crystalline tiotropium bromide monohydrate", it is noted that while the inventor may be his/her own lexicographer, claims 1-4 do not contain any of the physical data that particularly points out and distinctly claims the product that Applicant regards as his invention, i.e. no claim provides at least the ten strongest peaks of the X-ray diffraction data for the specific crystalline form of tiotropium bromide prepared. "Monoclinic crystalline... monohydrate" is not a limiting element and does not define a difference in the crystalline form of hydrates of tiotropium bromide over any other crystalline forms. In crystallography, when describing crystal systems, one refers to the dimensions of the crystal lattice in terms of three vectors, and the term "monoclinic" merely refers to a crystal that has three vectors of unequal length. It is the XRDP, DSC, and IR data that distinguishes Applicants' invention from the prior art, not the term "monoclinic." For example, without XRD data in the claims, it is impossible to distinguish Applicants' "monoclinic" crystalline monohydrate form from any other crystalline monohydrate of the prior art, since there is no data in the claims to distinguish Applicants' crystalline form from the other known crystalline monohydrates of the compound.

According to Brittain, "for routine work.., one typically compares the powder pattern of the analyte to that of reference materials to establish polymorphic identity." Since every compound produces its own characteristic powder diffraction pattern owing the unique crystallography of its structure, powder X-ray diffraction is clearly the most powerful and fundamental tool for a specification of the polymorphic identity of the analyte. Moreover, the U.S.P. general chapter on X-ray diffraction states that the identity is established if the scattering angles of the ten strongest reflections obtained for an analyte agree to within +/- 0.20 degrees

with that of the reference material, and if the relative intensities of these reflections do not vary by more than 20 percent (see Brittain in "Polymorphism in Pharmaceutical Solids," p.236).

Claims 1-4 fail to recite any X-ray diffraction peaks or at a minimum, ten peaks. The recitation of no peaks or less than ten peaks is not specific enough to particularly point out and distinctly claim the product that Applicant regards as his invention. The claims do not conform to the general practice in the art according to Brittain, i.e. including at least data for the 10 strongest peaks. Claims 1-4 do not contain any of the physical data that particularly points out and distinctly claims the product, crystalline "monohydrate" of tiotropium monohydrate that Applicant regards as his invention, i.e. no claim provides at least the ten strongest peaks of the X-ray diffraction data, or DSC, or IR spectra. For example, without this physical data, it is impossible to distinguish Applicants' "monoclinic" crystalline form from any other crystalline monohydrate form, since there is no data in the claims to distinguish Applicants' crystalline monohydrate from any other crystalline monohydrate. It is suggested that the claims be amended to include at least ten of the strongest peaks of the x-ray diffraction data for the intended crystalline "monohydrate" claimed. However, additional data such as the compound melting temperature, DSC thermogram data and infrared spectrum data supported in the instant specification could also be included in order to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible

harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 1-4 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,777,423 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because Applicants have previously patented crystalline tiotropium monohydrate with the endothermic peak and IR spectra as recited in claims 1-3 of the '423 patent. Furthermore, Applicants have also patented

monoclinic crystalline tiotropium bromide monohydrate with the dimensions recited in claims 4-6 of the '423 patent. Applicants have not provided any data to distinguish the instant claims from the previously patented claims, particularly since they are claiming the same monohydrate form in a monoclinic crystal system.

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent.

Conclusion

10. In conclusion, claims 1-4 and 9-21 are pending, claims 9-21 are currently withdrawn, and claims 1-4 currently stand rejected.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Coppins whose telephone number is 571.272.0680. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane can be reached on 571.272.0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Janet L. Coppins
February 5, 2007

KAMAL A. SAEED, PH.D.
PRIMARY EXAMINER

Joseph K. McKane
SPE, Art Unit 1626